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Predicting Mortality After Myocardial Infarction From the Response of RR Variability to Antiarrhythmic Drug Therapy

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Objectives. **This study was designed to test the hypothesis that antiarrhythmic drugs that decrease RR variability will predict all-cause mortality during follow-up after myocardial infarction.**

Background. **RR variability, a noninvasive indicator of autonomic nervous system activity, predicts death after acute myocardial infarction independently of other risk predictors and changes substantially in response to some drugs. A previous study in patients with chronic heart disease and frequent ventricular premature complexes reported that flecainide decreased vagal modulation of RR intervals but amiodarone did not. The investigators of that study speculated that changes in RR variability during antiarrhythmic drug therapy predict an increased mortality rate during long-term drug treatment. To explore this hypothesis further, we compared the effects of encainide and flecainide, which increase long-term mortality substantially, on RR variability with the effects of placebo and moricizine, which have no significant effect on mortality during long-term treatment of unsustained ventricular arrhythmias after myocardial infarction.**

Methods. **The 24-h power spectral density was computed from the baseline electrocardiographic recordings and drug evaluation tapes, and six frequency domain measures of RR variability were calculated: ultra-low frequency (<0.0033 Hz), very low frequency (0.0033 to <0.04 Hz), low frequency (0.04 to <0.15 Hz) and high frequency power (0.15 to <0.40 Hz), plus total power (<0.40 Hz) and the ratio of low to high frequency power. Changes in power spectral measures were related to drug treatment and to mortality.**

Results. **In the placebo group, values for RR interval and RR variability increased because of recovery from the effects of acute myocardial infarction. Contrasting placebo treatment with all three active antiarrhythmic drug treatments taken together showed that of all the measures of RR variability, only NN50, pNN50 and low frequency power changed significantly during drug treatment (Bonferroni adjusted p value <0.025); these variables all decreased during drug therapy. Contrasting encainide and flecainide with moricizine, we found that the encainide and flecainide groups taken together showed a larger decrease in dLF than moricizine, but the difference was of borderline significance (Bonferroni adjusted p value <0.08). Survival was significantly worse in the groups treated with encainide and flecainide than in the groups treated with placebo or moricizine (relative risk >2.0, adjusted $p < 0.05$). The antiarrhythmic drug-induced change in measures of RR variability was not a significant predictor of all-cause mortality during a year of follow-up after myocardial infarction.**

Conclusions. **Encainide, flecainide and moricizine all caused a decrease in RR variability in patients studied ~1 month after acute myocardial infarction. Encainide and flecainide caused a significant increase in mortality rates; placebo and moricizine did not. Baseline measurements of RR variability also predicted all-cause mortality after myocardial infarction. The decrease in RR variability produced by the three antiarrhythmic drugs did not predict mortality during follow-up.**

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RR variability, a noninvasive indicator of autonomic nervous system activity, predicts death after acute myocardial infarction independently of other risk predictors (1–6). Unlike other major risk predictors, such as left ventricular ejection fraction, RR variability is a dynamic variable, decreasing immediately after myocardial infarction and then recovering over a few months (7,8). Also, RR variability changes substantially in response to some drugs. In normal subjects, RR variability increases in response to atenolol and digoxin but does not change in response to diltiazem or enalapril (9,10). In patients with chronic heart disease and frequent ventricular premature complexes, Zuanetti et al. (11) reported that flecainide decreased the vagal modulation of RR intervals, but amiodarone did not. These investigators speculated that changes in RR variability that indicate a decrease in vagal modulation may predict an increased likelihood of mortality during long-term drug treatment. To explore this hypothesis further, we compared the effects on RR variability of encainide and flecainide, which increase

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mortality substantially (12,13), with the effects of moricizine, which has no significant effect on mortality during long-term treatment of postinfarction unsustained ventricular arrhythmias (14). Also, we tested the hypothesis that the effect of drug on RR variability predicted subsequent mortality.

Methods

Patient selection. To evaluate the effects of encainide, flecainide and moricizine on RR variability, we used 24-h electrocardiographic (ECG) recordings from the Cardiac Arrhythmia Pilot Study (CAPS) (15,16), which recruited patients in a 6- to 60-day period after acute myocardial infarction. To qualify, patients had to have ≥10 ventricular premature complexes/h on a 24-h continuous ECG recording (15). After patients were enrolled and baseline data were obtained, they were randomized to one of five treatment limbs, four with active antiarrhythmic drug and one with placebo. Within the active treatment limbs, drug and dose changes were permitted to achieve 70% suppression of ventricular premature complexes (15). To control for recovery of RR variability as a function of time (8), we used data from the group randomized to placebo. To avoid bias due to drug responsiveness, we used the response to the first dose of the first drug in three active treatment limbs (encainide, flecainide and moricizine). Imipramine was not evaluated in this study because there are no randomized controlled studies that evaluate its effect on mortality.

Processing of 24-h ECG recordings. The 24-h recordings were digitized on a Marquette 8000 Holter system and submitted to the standard Marquette algorithms for QRS labeling and editing (version 5.8 software). The data files were then transferred by high speed link from the Marquette scanner to a Sun workstation where a second stage of editing was done, using algorithms developed at Columbia University, to find and correct any remaining errors in QRS labeling that adversely affect measurement of heart period variability. For a tape to be eligible for this study, we required it to have ≥12 h of analyzable data and at least half of the night-time (00:00 to 05:00) and daytime (07:30 to 21:30) periods analyzable. At least 50% of the recording had to be sinus rhythm.

Power spectral analysis. After editing was completed, the heart period power spectrum was computed over a 24-h interval using a previously described method (17,18). First, a regularly spaced time series was derived from the RR intervals by sampling the irregularly spaced series defined by the succession of normal RR intervals. For 24-h ECG recordings, 2^{18} points were sampled. A "boxcar" low pass filter with a window twice the sampling interval was then applied. Gaps in the time series resulting from noise or ectopic complexes were filled in by linear splining. A fast Fourier transform was computed and the resulting power spectrum was corrected for the attenuating effects of both the filtering and the sampling (17,18). The effective lower end of the frequency range for this method was 1.16×10^{-5} for 24 h. The upper end of the frequency range was 0.40 Hz.

Time and frequency domain measures of heart period variability. Frequency domain measures of heart period variability were computed by integrating over their frequency intervals. Six frequency domain measures were calculated from spectral analysis of 24 h of RR interval data. We computed the 24-h power spectral density and calculated the power within four frequency bands: 1) <0.0033 Hz = ultra-low frequency power, 2) 0.0033 to <0.04 Hz = very low frequency power, 3) 0.04 to <0.15 Hz = low frequency power, and 4) 0.15 to 0.40 Hz = high frequency power (5). In addition, we calculated total power (<0.40 Hz) and the ratio of low to high frequency power (5).

In the time domain, we computed NN50, a variable that reflects vagal modulation of NN intervals, as the number of differences between successive normal RR intervals exceeding 50 ms. We computed the proportion of differences between adjacent normal RR intervals that are >50 ms, pNN50, and the root mean square successive difference, as described previously (7).

Statistical procedures. Before statistical analyses, the power spectral measures of RR variability were log transformed because their distributions were strongly skewed. The data were summarized as the mean value ± SD of the log-transformed data. Baseline (predrug) values were compared among treatment groups by using one-way analysis of variance for continuous variables and chi-square analysis for discrete variables. Differences in power between baseline and initiation of treatment were also compared using one-way analyses of covariance with two a priori contrasts being tested: 1) placebo versus active antiarrhythmic drug treatment, and 2) encainide and flecainide versus moricizine treatment. The two covariates used in these analyses were time from myocardial infarction to baseline tape and time from baseline tape to first dosing tape. The Bonferroni adjustment was used for these multiple contrasts at an overall alpha level of 0.05.

Kaplan-Meier survival analysis. We calculated Kaplan-Meier curves (19) to display graphically the cumulative mortality rates of the CAPS patients over the 12-month period after the 24-h ECG and to test the association between NN50 and low frequency power measurements and all-cause mortality. The significance of differences between curves was evaluated with the log-rank test (20). For these analyses, RR variability measures were dichotomized using cut points obtained from the Multicenter Postinfarction Program (MPIP) patient groups (5).

Dichotomization of dNN50 and dLF. The differences in log-transformed values for NN50 (dNN50) or low frequency power (dLF) between the baseline (drug-free) 24-h ECG and the 24-h ECG done during treatment were calculated for each patient. Values for dNN50 and dLF were used as dichotomous predictors in survival analyses. Dichotomization permits an easily understandable relative risk for death to be calculated from the Cox regression coefficient (21). The value at which to dichotomize was determined by calculating Cox hazard ratios at every possible dichotomization point.

Table 1. Reasons for Exclusion of 24-h Electrocardiographic (ECG) Data

	Patient Treatment Group				
	Placebo	Flecainide	Encainide	Moricizine	Total
Patients randomized to group	100	103	99	98	400
Reasons for exclusion					
ECG tape missing	3	5	2	8	18
ECG tape ineligible	2	6	0	1	9
Patient never had both tapes recorded	5	4	4	5	18
Patients remaining for analysis	90	88	93	84	355

The dichotomization point that yielded the largest hazard ratio was obtained and rounded to the nearest multiple of 0.1. Patients with values at or below the dichotomization point are hypothesized to be at higher risk than patients with values above it. The P2L BMDP computer program was used to carry out the Cox survival analyses (22).

Results

Baseline characteristics of the sample. Table 1 presents the reasons why the ECG tapes from 45 of the 400 randomized patients could not be used. Overall, 11% of the patients were excluded from the analysis because of problems with these tapes. There were no differences among the treatment groups with respect to such exclusion.

Table 2 lists the baseline characteristics for the four treatment groups. The median time from the index myocardial infarction to the baseline 24-h ECG for all four treatment groups together was 25 days (range 5 to 63). The interval between the index myocardial infarction and the baseline 24-h ECG did not vary significantly among the four groups. There was no significant difference among the groups for the time between the baseline 24-h ECG recording and the first drug assessment recording. After adjustment for multiple testing, there were no significant differences at baseline among the four groups with respect to time or frequency domain measures of RR variability.

Drug effects on RR interval and RR variability. Table 3 shows the effects of treatment with the first dose of the first treatment on the 24-h average RR interval and various time

Table 2. Comparison of Baseline Clinical Characteristics Among the Treatment Groups (n = 355)

	Placebo (n = 90)	Flecainide (n = 88)	Encainide (n = 93)	Moricizine (n = 84)
Age (yr)	60 ± 9	59 ± 9	59 ± 9	59 ± 9
Male (%)	80	80	86	85
CAPS baseline				
Previous myocardial infarction (%)	32.2	30.7	26.9	27.4
History of congestive heart failure (%)	4.5	3.4	6.5	4.9
Diabetes (%)	15.6	25.0	17.2	13.1
Left ventricular ejection fraction	0.45 ± 0.12	0.46 ± 0.13	0.45 ± 0.12	0.45 ± 0.14
Rales (%)	3.4	7.1	9.2	7.5
ln ventricular premature complexes/h	4.05 ± 1.08	4.03 ± 1.11	3.87 ± 1.20	4.09 ± 1.24
Medications (%)				
Digitalis	24.7	21.1	19.7	23.7
Diuretic drug	35.8	39.4	40.0	43.4
Beta-adrenergic blocker	43.2	35.2	39.5	31.6
Calcium channel blocker	37.0	33.8	44.6	36.8
Timing of 24-h ECG recordings				
Days from myocardial infarction to baseline tape	24 (6–60)	17 (6–63)	30 (5–62)	31 (6–60)
Days from baseline tape to the first drug assessment tape	11 (6–39)	10 (6–25)	11 (6–29)	11 (4–22)
Measures of RR variability				
Average normal to normal RR interval	787 ± 147	837 ± 155	849 ± 153	814 ± 135
ln ultra-low frequency power (ms^2)*	8.47 ± 0.93	8.44 ± 0.40	8.69 ± 0.85	8.48 ± 0.94
ln very low frequency power (ms^2)*	6.16 ± 1.30	6.51 ± 1.15	6.53 ± 1.22	6.45 ± 1.09
ln low frequency power (ms^2)*	4.89 ± 1.38	5.24 ± 1.32	5.26 ± 1.25	5.21 ± 1.40
ln high frequency power (ms^2)*	3.95 ± 1.18	4.35 ± 1.25	4.32 ± 1.04	4.35 ± 1.25
ln total power (ms^2)*	8.64 ± 0.90	8.66 ± 0.95	8.88 ± 0.95	8.69 ± 0.94
Ratio of low to high frequency power	3.35 ± 2.55	3.14 ± 2.20	3.27 ± 2.28	3.09 ± 1.86

Unless otherwise indicated, values are presented as mean value ± SD or median (range). *Geometric means may be obtained for these values in the original scale of measurement (ms^2) by exp(mean of the logarithmically transformed values). The 95% confidence limits for the geometric mean can be calculated by exp(L ± 1.96 × SE), where L is the mean logarithm and SE is the corresponding standard error. ln = natural logarithm.

Table 3. Change in Measures of RR Variability Between Baseline and Dosing Tapes (n = 355)

	Placebo (n = 90)	Flecainide (n = 88)	Encainide (n = 93)	Moricizine (n = 84)
Change in time domain measures of RR variability				
Average normal to normal RR interval	1.02	1.02	1.03	0.99
	(1.0,1.5)	(0.99,1.04)	(1.00,1.04)	(0.97,1.02)
NN50*	1.55	1.06	0.96	0.78
	(1.15,2.10)	(0.77,1.44)	(0.71,1.30)	(0.57,1.08)
pNN50†	1.59	1.02	0.91	0.79
	(1.17,2.16)	(0.73,1.41)	(0.67,1.24)	(0.58,1.08)
Root mean square of successive difference	1.07	0.97	1.01	0.99
	(0.98,1.17)	(0.87,1.08)	(0.93,1.09)	(0.91,1.07)
Change in power spectral measures of RR variability				
Ultra-low frequency power	1.06	1.02	1.00	1.01
	(1.01,1.11)	(0.95,1.09)	(0.95,1.05)	(0.96,1.07)
Very low frequency power	1.12	0.86	0.96	0.96
	(0.90,1.02)	(0.79,0.93)	(0.92,1.01)	(1.06,1.18)
Low frequency power	1.09	0.85	0.96	0.98
	(1.02,1.16)	(0.76,0.93)	(0.89,1.01)	(0.90,1.06)
High frequency power	1.08	0.99	1.05	0.99
	(0.99,1.17)	(0.89,1.09)	(0.97,1.12)	(0.92,1.07)
Total power	1.06	1.00	1.00	1.00
	(1.00,1.11)	(0.93,1.07)	(0.95,1.04)	(0.95,1.05)
Ratio of low to high frequency power	1.03	0.70	0.80	0.97
	(0.90,1.18)	(0.60,0.81)	(0.71,0.90)	(0.87,1.08)

*The number of differences between adjacent normal RR intervals that are >50 ms. †The proportion of differences between adjacent normal RR intervals that are >50 ms. Quantities not in parentheses are antilogarithms of mean differences between logarithmically transformed dosing tape and baseline tape values (that is, proportional changes); 1.06 can be read as a 6% increase and 0.94 as a 6% decrease. The values in parentheses are the corresponding 95% confidence limits. The 95% confidence limits were calculated by exp(L ± 1.96 × SE), where L is the mean of the differences between the logarithm during drug therapy and the logarithm of the baseline value and SE is the standard error of the differences.

and frequency domain measures of RR variability. In the placebo group, values for RR interval and RR variability increased because of recovery from the effects of acute myocardial infarction (8). The increase was larger for NN50 and pNN50 than for the other measures. Figure 1 shows the distribution of changes between the baseline 24-h ECG and the 24-h ECG used to evaluate the first treatment. Using analysis of covariance procedures and adjusting for time from myocardial infarction to baseline tape and time from baseline tape to first dosing tape, our a priori contrasts yielded the following results. Contrasting all three active antiarrhythmic drug treatments taken together with placebo treatment showed that of all the measures of RR variability, only NN50, pNN50 and low frequency power changed significantly during drug treatment (Bonferroni adjusted p value <0.025). These variables all decreased during drug therapy. Contrasting encainide and flecainide with moricizine, we found that encainide and flecainide taken together caused a larger decrease in dLF than moricizine, but the difference was borderline (Bonferroni adjusted p value <0.08).

Effect of drug treatment on all-cause mortality. To distinguish between the effect of drug and the effect of RR variability on mortality, we combined into one group patients on encainide or flecainide and combined into a second group patients on moricizine or placebo. We grouped patients receiving encainide and flecainide therapy together because in the Cardiac Arrhythmia Suppression Trial (CAST) (13) these drugs were associated with similar increases in mortality rates over those associated with placebo treatment. We grouped patients receiving placebo and moricizine together because in CAST II (14) such patients had similar mortality rates during long-term treatment. Figure 2 compares the cumulative mortality rate for the flecainide-encainide group with that of the placebo-moricizine group in the CAPS sample. The 1-year mortality rate for the placebo-moricizine group was 6.4% compared with 12.3% for the encainide-flecainide group.

Does NN50 or low frequency power, as measured on the baseline or first dosing 24-h ECG, predict all-cause mortality during follow-up? Kaplan-Meier curves were calculated (Fig. 3) to show the cumulative mortality rate for patients with high and low frequency power (left) and high and low NN50 (right) measured in the baseline recordings. The cut points for low frequency power and low NN50 were determined by using the MPIP data (5). For both baseline measures of RR variability, there was a large and statistically significant difference in the cumulative mortality rate between the high and low groups ($p < 0.01$ by the log-rank test). Figure 4 shows that during antiarrhythmic drug treatment, low values for low frequency power (left) and low NN50 (right) still predict all-cause mortality over the year of follow-up. However, the association between treatment values of NN50 and mortality is weaker than the association between baseline values of NN50 and mortality.

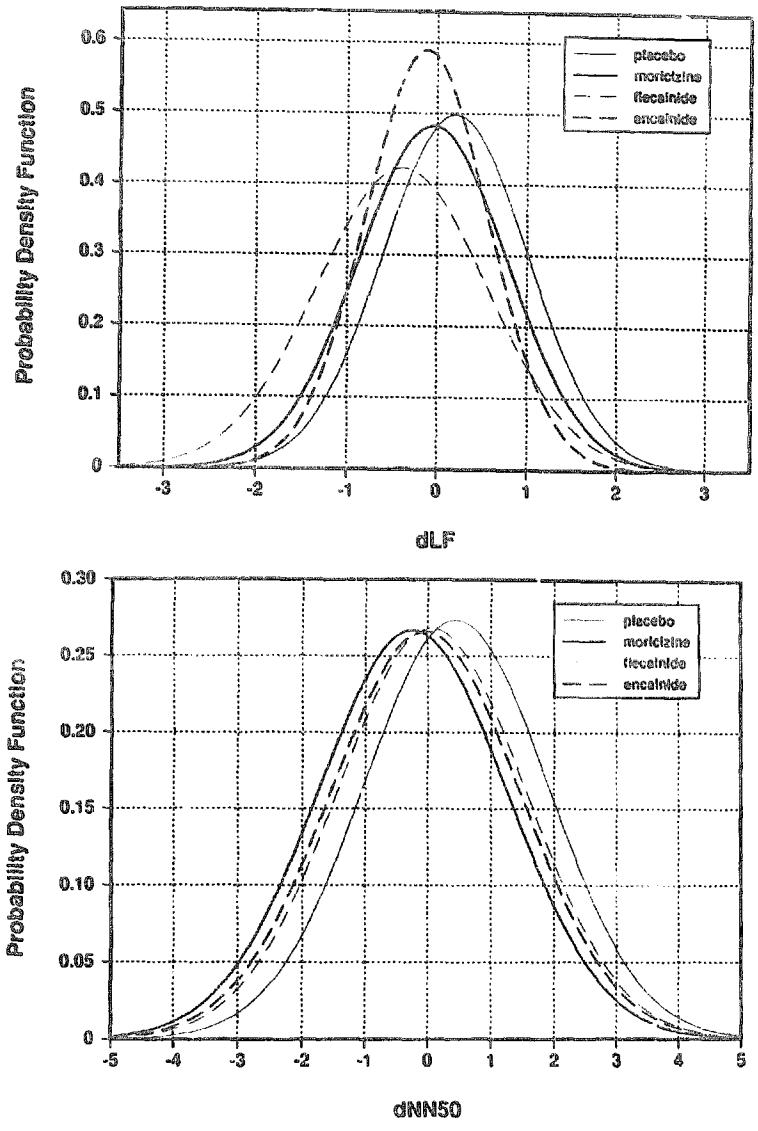
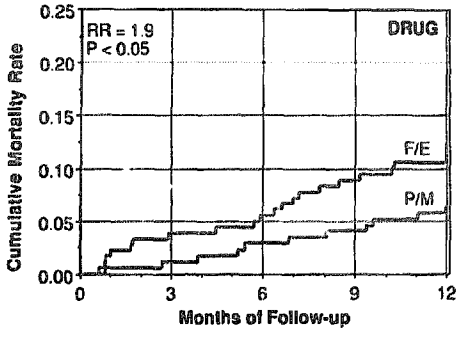


Figure 1. Effect of antiarrhythmic drugs on dLF (top) and dNN50 (bottom). The X axis is the change in the measure of RR variability in units of natural logarithms. The Y axis is the probability density function for a normal distribution with the same mean and standard deviation as found in the Cardiac Arrhythmia Pilot Study (15,16) sample. These curves are centered at the mean values of the distributions for the four treatment groups: placebo, moricizine, encainide and flecainide. For the placebo group, the average change is positive; for the three groups treated with active drug, the average change is much less positive or negative.

Dichotomization of dNN50 and dLF. The value of dNN50 at the optimal dichotomization point, rounded to the nearest multiple of 0.1, was −1.3; 13.2% of patients had values at or below the cut point and 86.8% had values above the cut point. The value of dLF at the optimal dichotomization point, rounded to the nearest multiple of 0.1, was −0.7. Using this value, 15.2% of patients had values at or below the cut point and 84.8% had values above it.

Does the change in RR variability due to antiarrhythmic drug treatment predict all-cause mortality during follow-up? Because we had only 34 end points, we restricted the analyses to the evaluation of two measures of RR variability as predictor variables and to one end point, namely, all-cause mortality. The dNN50 value was chosen because it decreased significantly during antiarrhythmic drug therapy and was the study variable used that suggested the primary hypothesis that we are testing (11). We chose dLF power because low frequency power was the only power spectral measure that decreased significantly during drug treatment,

Figure 2. Comparison of mortality in the group treated with flecainide or encainide (F/E) and the group treated with placebo or moricizine (P/M). The mortality rate was 1.9 times higher in the flecainide-encainide group ($p < 0.05$) compared with the placebo-moricizine group. The numbers of patients at the start of follow-up and the numbers known to be alive and being followed up after 6 months and 1 year are as follows: flecainide-encainide group 181, 171 and 131, placebo-moricizine group 174, 169 and 131, respectively.



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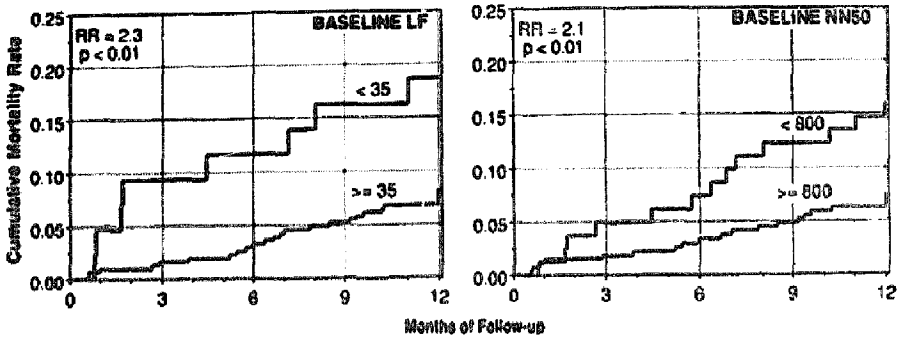

Figure 3. Left, Kaplan-Meier curves comparing the cumulative all-cause mortality rate for the group with low values of low frequency power (<35 ms^2) measured on the baseline 24-h electrocardiogram (ECG) with the group with high values of low frequency power (≥35 ms^2). The number of patients at the start of follow-up and the number of patients known to be alive and being followed up after 6 months and 1 year are as follows: group with high values of low frequency power 312, 302 and 237; group with low values of low frequency power 43, 38 and 25, respectively. Right, Kaplan-Meier curves comparing the cumulative all-cause mortality for the group with low values for NN50 (<800) measured on the baseline 24-h ECG with the group with high values of NN50 (≥800). The numbers of patients at the start of follow-up and the numbers known to be alive and being followed up after 6 months and 1 year are as follows: group with high values of NN50 273, 264 and 208; group with low values of NN50 82, 76 and 54, respectively. There is a large and significant difference between the groups with low values for low frequency power or NN50 and the groups with high values.

adjusting for time from myocardial infarction to baseline tape and time from baseline tape to first dosing tape.

Kaplan-Meier curves were calculated (Fig. 5) to show the cumulative mortality rates in the groups categorized by the response of low frequency power or NN50 to drug therapy. Neither dLF power nor dNN50 had predictive value for mortality.

Discussion

Drugs with class I antiarrhythmic action decrease NN50. Previous investigators (7,23) showed that NN50 is a sensitive and reliable index of cardiac parasympathetic activity. In 1991, Zuanetti et al. (11) published a study that evaluated three issues: 1) the reproducibility of NN50 in patients with

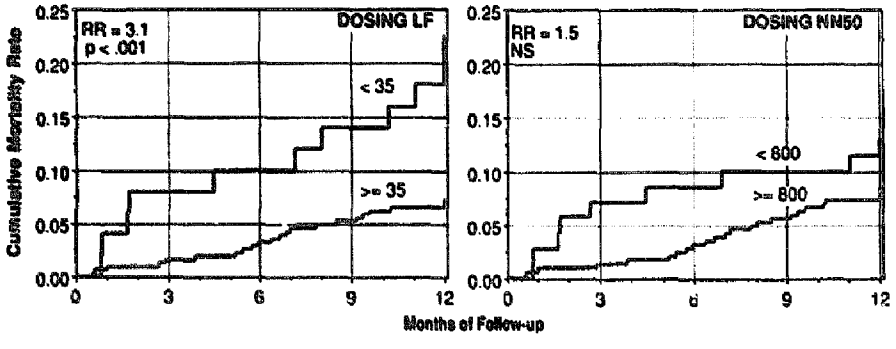

Figure 4. Left. Kaplan-Meier curves comparing the cumulative all-cause mortality for the group with low values of low frequency (LF) power (<35 ms^2) measured on the first 24-h electrocardiogram (ECG) during treatment with the group with high values of low frequency power (≥35 ms^2). The numbers of patients at the start of follow-up and the numbers known to be alive and being followed up after 6 months and 1 year are as follows: group with high values of low frequency power 312, 302 and 237; group with low values of low frequency power 43, 38 and 25, respectively. **Right.** Kaplan-Meier curves comparing the cumulative all-cause mortality for the group with low values of NN50 (<800) measured on the first 24-h ECG during treatment with the group with high values of NN50 (≥800). The numbers of patients at the start of follow-up and the numbers known to be alive and being followed up after 6 months and 1 year are as follows: group with high values of NN50 273, 264 and 208; group with low values of NN50 82, 76 and 54, respectively. The mortality rate is substantially higher for the groups with low values for low frequency power or NN50. The difference is significant for low frequency power and borderline for NN50.

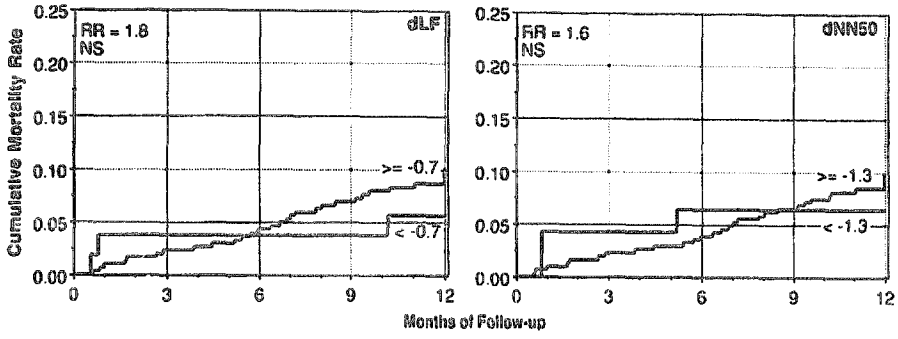

Figure 5. **Left,** Kaplan-Meier curves comparing the cumulative all-cause mortality for the group with low values of dLF (<-0.70 ln ms^2) (the difference between baseline values and the values found in the first 24-h electrocardiogram [ECG] during treatment) with the group with high values dLF (≥-0.70 ln ms^2). The numbers of patients at the start of follow-up and the numbers known to be alive and being followed up after 6 months and 1 year are as follows: group with high values for dLF 312, 302 and 237; group with low values for dLF 43, 38 and 25, respectively. **Right,** Kaplan-Meier curves comparing the cumulative all-cause mortality for the group with low values of dNN50 (<-1.3 ln counts) measured on the first 24-h ECG during treatment with the group with high values of NN50 (≥-1.3 ln counts). The numbers of patients at the start of follow-up and the numbers known to be alive and being followed up after 6 months and 1 year are as follows: group with high values of NN50 273, 264 and 208; group with low values of NN50 82, 76 and 54, respectively. The association between dLF or dNN50 and all-cause mortality is not statistically significant. Furthermore, there is a tendency for the "low risk group" to have a higher 1-year mortality rate.

frequent ventricular premature complexes, 2) the effect of arrhythmia suppression on NN50, and 3) the link between antiarrhythmic drug action and its effect on NN50. They found that NN50 for a 24-h period was reproducible between tapes recorded at a median interval of 192 days (range 8 to 910) and that the effect of three antiarrhythmic drugs on NN50 was independent of their effect on the frequency of ventricular premature complexes. Also, in 56 patients, they found substantial differences among the three antiarrhythmic drugs with respect to effect on NN50. For amiodarone, the median percent change in NN50 was −8% (a change that was not significantly different from baseline values). For two drugs with class IC antiarrhythmic action, flecainide and propafenone, the median percent changes were −56% and −64%, respectively. These workers gave a sophisticated discussion of how antiarrhythmic drugs might decrease NN50. They cited work in animal models that suggested that ventricular arrhythmias could increase efferent sympathetic activity (24,25), an effect that would reduce NN50. Their data did not support a hypothesis that ventricular arrhythmias cause a decrease in NN50 because there was no correlation between NN50 and the frequency of ventricular premature complexes at baseline and NN50 was not affected when ventricular arrhythmias were suppressed. They speculated that drugs might interact with the autonomic nervous system directly or indirectly by means of autonomic reflexes activated by drug-induced decreases in cardiac contractility or peripheral vasodilation.

Drug-induced changes on NN50 hypothesized to predict death. Zuanetti et al. (11) speculated that because low values for measures of RR variability have been associated with an increased mortality rate after myocardial infarction (1–5), the decrease in NN50 found during flecainide and propafenone treatment might reflect a poor prognosis; that is, a drug-induced decrease in NN50 might be an indicator of an increased mortality risk during treatment. They pointed out that flecainide therapy was associated with increased mortality rates in CAST (12,13). Following this line of reasoning, flecainide and propafenone would be expected to be harmful and amiodarone not harmful.

Flecainide, encainide and moricizine all decrease NN50 and low frequency power. We conducted our study in the CAPS sample to test the hypothesis put forward by Zuanetti et al. (11). We studied the three drugs that have a known effect on all-cause mortality. In CAST (12,13), flecainide and encainide were found to increase the mortality rate during long-term therapy in a randomized comparison with placebo-treated control patients. Moricizine-treated patients had a mortality rate during long-term therapy that was not significantly different from that in the placebo-treated control patients (14). We showed that compared with placebo treatment and adjusted for the recovery in measures of RR variability that occurs after acute myocardial infarction (8), all three antiarrhythmic drugs caused a decrease in various measures of RR variability. We selected two measures, NN50 and low frequency power, for the formal test of our hypothesis. dNN50 was chosen because NN50 was the variable used in the study that suggested the primary hypothesis that we are testing and it decreased significantly during antiarrhythmic drug therapy; dLF power was chosen because low frequency power was the only power spectral measure that decreased significantly during drug treatment.

Between the two 24-h ECG recordings, there was a 55% increase in NN50 in the placebo group (Table 3) due to the recovery that takes place after infarction (8). Relative to the placebo group, the drug groups showed a decrease in NN50 that was 49%, 59% and 77% for flecainide, encainide and moricizine, respectively. Between the two 24-h ECG recordings, one at baseline and one during drug therapy, there was a 9% increase in low frequency power in the placebo group. Relative to the placebo group, the drug groups showed a decrease in low frequency power that was 24%, 13% and 11% for flecainide, encainide and moricizine, respectively. Thus, all three drugs caused a decrease in NN50 and in low frequency power.

Drug-induced decreases in NN50 or low frequency power do not predict death. As expected from previous studies (1–5,26) in other postinfarction samples, baseline values of low frequency power and NN50, which reflect the severity of circulatory dysfunction, were excellent predictors of all-cause mortality after myocardial infarction. The placebo-moricizine group had a significantly lower mortality rate than did the flecainide-encainide group. Also, the values of low frequency power and NN50 found during antiarrhythmic drug therapy predicted mortality during the 1st year of follow-up. However, the decrease in NN50 and low frequency power caused by drug treatment (that is, the difference between the first drug treatment tape and the baseline tape) was not associated with the mortality rate during a year of treatment. This suggests that although encainide and flecainide are associated with an increased mortality rate and a decrease in NN50 and low frequency power, and although the baseline values and treatment values for low frequency power and NN50 are excellent predictors of mortality, the increased mortality rate is not mediated by the drug-induced changes in RR variability. Thus, it appears for the three drugs studied that the decrease in NN50 or low frequency power due to antiarrhythmic drug therapy itself was not a significant predictor of mortality.

The current findings indicate that the changes in NN50 and low frequency power caused by treatment with flecainide, encainide or moricizine cannot be used to predict death during a year of treatment with these drugs. This finding does not mean that drug-induced changes in measures of RR variability do not have prognostic significance in other disease states or for other drugs. However, it indicates that relations between drug effects on RR variability and outcomes will have to be established in data sets that have outcome data available.

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